Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IL2006/000017

International filing date: 05 January 2006 (05.01.2006)

Document type: Certified copy of priority document

Document details: Country/Office: IL
Number: 166183
Filing date: 06 January 2005 (06.01.2005)

Date of receipt at the International Bureau: 08 February 2006 (08.02.2006)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

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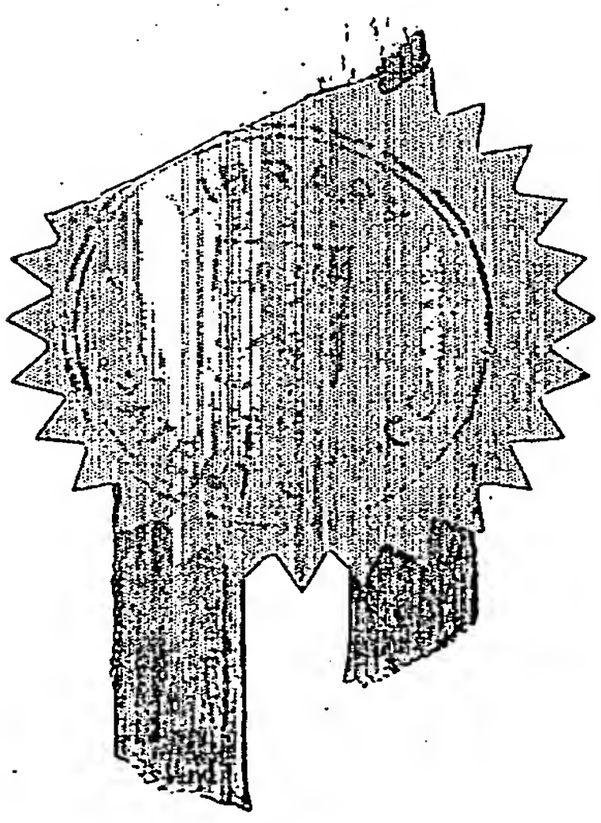

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Application for Patent

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NOVEL DIAGNOSTIC AND IMAGING TECHNIQUES OF THE GI TRACT

מבקש בזאת כי ינתן עליה פטנט

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שיטות חדשות לאבחון והדמיה של מערכת העיכול

NOVEL DIAGNOSTIC AND IMAGING TECHNIQUES OF THE GI TRACT

Field of the Invention

The present invention relates to the field of medical diagnostics. More specifically, the present invention relates to diagnostic devices and imaging of the gastrointestinal tract.

Background of the Invention

All publications mentioned throughout this application are fully incorporated herein by reference, including all references cited therein.

Physical examination is an important part of anamnesis and is an effective tool in medicine, enabling health care professionals to unveil the correct diagnosis. However, this tool is handicapped when internal organs are to be examined. Thus numerous techniques have been developed that afford reasonable imaging of the human interior, with or without the need of contrast medium to obtain higher resolution and better visualisation. These non-invasive methods are highly valued by the end users – the practicing doctors.

Gastrointestinal (GI) tract, for being an open system, allows the introduction of imaging probes and contrasts relatively non-invasively, namely, *per os* or *pro rectum*. Oral administration of markers has significant advantage over rectal, since it enables physiologic transit of the marker to the area of interest, including physiological, pathophysiological, metabolism, absorption, and detoxification sites, besides allowing the transit time of a molecule or a vehicle/device to be followed through the GI system.

Although a breakthrough when originally developed, the oral administration of markers has now revealed some downsides. Upon administration, a marker first encounters the stomach, wherefrom it is cleared at variable rates. This can give rise to internal method variability, thus diminishing the accuracy and signal-to-noise ratio of a diagnostic or imaging test. There are other examples of inaccuracies. One of them is Octreoscan® (Mallinkrodt Medical Inc.), a somatostatin analogue. This material is In111-labelled octreotide – relatively

metabolically stable somatostatin, and it is normally injected to reveal neuroendocrine carcinomas. However, its ability to bind somatostatin receptors enables imaging of *all* somatostatin receptor-expressing cancers, only some of which are found in the GI tract, like carcinoid, or Zollinger-Ellison syndrome. Another example is the assessment of upper intestinal transit time with the use of technetium, or any other radioactive isotope, which is highly encumbered by the variance in gastric emptying.

Another important problem is the assessment of the continuity of the lumen of the gastrointestinal tract, i.e. the timely determination of any obstructions inside the intestinal lumen. Currently, small bowel transit time is estimated via the breath hydrogen method in conjunction with scintigraphy, but the results are inaccurate due to variable gastric emptying, and the technique cumbersome due to the use of nuclear medicine. Colonic integrity is evaluated with total colon enema wash, followed by barium enema and computer tomography (CT) or simple radiology. And colonoscopy is still the procedure of choice for unequivocal diagnosis.

An additional approach to visualize the GI tract is Magnetic Resonance Imaging (MRI). MRI is an imaging technique used primarily in medical settings to produce high quality images of the inside of the human body. MRI is based on the principles of nuclear magnetic resonance (NMR), a spectroscopic technique used by scientists to obtain microscopic chemical and physical information about molecules. Unlike computed tomography (CT) scanning, MRI does not make use of ionizing radiation and neither requires iodinated contrast material (known for causing hypersensitivity reactions and nephrotoxicity in susceptible patients) in order to distinguish normal from pathologic tissue. Rather, the technique is based on the difference in the number of protons contained within hydrogen-rich molecules in the body (water, proteins, lipids, and other macromolecules) which determines the recorded image quality and makes possible the distinction between normal and pathological tissue, nerves, tumors, infections, and flowing blood within

vascular structures. Despite the advantages of multiplanar imaging and sequential varieties, there has been little attempt to utilize MRI for diagnosing diseases of the small intestine. This is primarily due to the lack of a suitable, cost-effective oral contrast agent. In fact, some researchers have attempted conventional MRI for evaluation of the gastrointestinal tract [Chou, C.K. *et al.* (1994a) MRI manifestations of gastrointestinal wall thickening. *Abdom Imaging*; 19:389-394; Chou, C.K. *et al.* (1994b) MRI manifestations of gastrointestinal lymphoma. *Abdom Imaging*; 19:495-500; Ha, H.K. *et al.* (1998) Application of MRI for small intestinal diseases. *J Magn Reson Imaging*; 8:375-383; Madsen, S.M. *et al.* (1997) Magnetic resonance imaging of Crohn disease: early recognition of treatment response and relapse. *Abdom Imaging*; 22:164-166; Beers, B.V. *et al.* (1994) MRI of complicated anal fistulae: comparison with digital examination. *J Comput Assist Tomogr*; 18:87-90]. However, because of the long acquisition time, bowel marking is very poor due to motion artifacts and/or peristaltic bowel movements.

A different but important diagnostic tool is the measuring of intragastric pH. This is normally performed by insertion of indwelling pH electrodes, or radiotelemetry indigestible capsule which bears chemical/electrical sensor for pH. The disadvantages of these methods are two-way (at least). The capsule is prone to leaving the stomach prematurely, and the planting indwelling electrode is not a simple and palatable procedure. In addition, it is known that the pH is not the same in different regions of the stomach, and such an electrode will not give the full clinical picture unless is subjected to relocations inside the patient's stomach.

Another important issue is gastrointestinal bleeding, which is extremely important to identify and locate, and in many cases it may be a matter of life and death. Obscured blood in the faeces is one the routine clinical checks performed "in bulk" in every medical centre. There are several home-test kits to reveal bleeding, however they suffer from great deal of inaccuracy, do not provide for exact locations of the bleeding, and frequently present false positive

results in haemorrhoids patients, which can be absolutely unaware of internal manifestations of them. As to date, no effective solution for this need is available, apart from gastroscopy and colonoscopy, however all small bowel bleedings remain undisclosed by these means.

US 6,120,803 describes an active agent dosage form adapted for gastric retention, comprised of an active agent, a polymeric matrix and at least one band of insoluble material circumscribing a portion of the surface of the polymer matrix. Said dosage form is adapted to be retained and deliver said active agent in the stomach. Moreover, it is also adapted to comprise a gastric-emptying delay agent. Nonetheless said dosage form does not allow imaging or follow up of the complete GI tract.

US 6,290,989 describes a delivery device which may be retained in the stomach for prolonged periods of time. It contains an expandable component, which causes the device to expand upon ingestion. Most importantly, it has no component which confers mechanical strength to the expanded device, and the retention time is said to be controllled by the rate of diffusion of the "gas" from the membrane.

WO 2004/032906 describes gastro-retentive dosage forms for prolonged delivery of levodopa and carbidopa-levodopa combinations, in the form of gas-expandable tablets. The goal of this dosage form is to be retained in the stomach enough time so that the active agent may be released and absorbed in the upper small intestine. Since it is intended for absorption of the active agent, said dosage form is not useful as a diagnostic device of the entire GI tract.

US 6,797,283 provides a multilayered dosage form which is gastro-retentive and adapted for prolonged delivery of an agent to the stomach. However, said device is not adapted for diagnostic of the GI tract beyond the stomach.

Diagnostic procedures currently used for digestive disorders are summarized below.

Laboratory tests:

- Fecal occult blood test: this test checks for occult blood in the stool.
- Stool culture: a stool culture checks for the presence of abnormal bacteria in the digestive tract that may cause diarrhea and other problems.

Imaging tests:

- Barium beefsteak meal: during this test, the patient eats a meal containing barium, allowing the radiologist to watch the stomach as it digests the meal. The amount of time it takes for the barium meal to be digested and leave the stomach gives the physician an idea of how well the stomach is working and helps to detect emptying problems that may not show up on the liquid barium X-ray.
- Colorectal transit study: this test shows how well food moves through the colon. The patient swallows capsules containing small markers which are visible on X-ray. The patient follows a high-fiber diet during the course of the test, and the movement of the markers through the colon is monitored with abdominal X-rays taken several times three to seven days after the capsule is swallowed.
- Computed tomography scan (CT or CAT scan): this diagnostic imaging procedure uses a combination of X-rays and computer technology to produce cross-sectional images, both horizontally and vertically, of the body.
- Defecography: defecography is an X-ray of the anorectal area that evaluates completeness of stool elimination, identifies anorectal abnormalities, and evaluates rectal muscle contractions and relaxation.
- Lower GI series (also called barium enema): the lower GI series examines the rectum, the large intestine, and the lower part of the small intestine. Barium, a metallic, chemical, chalky liquid used to coat the inside of organs so that they will show up on an X-ray, is given pro rectum as an enema. An X-ray of the abdomen shows strictures (narrowed areas), obstructions, and other problems.

- Magnetic Resonance Imaging (MRI): this is a diagnostic procedure that combines large magnets, radiofrequencies, and a computer to produce detailed images of organs and structures within the body. The test is painless, and does not involve exposure to radiation. However, because the MRI machine resembles a tunnel, some people are claustrophobic or unable to hold still during the test, and have to be given a sedative. Metal objects interfere with the MRI, so persons with pacemakers or metal clips or rods inside the body cannot have this test done.
- Oropharyngeal motility (swallowing) study: this is a study in which the patient is given small amounts of liquid containing barium to drink. Barium is a metallic chemical, a chalky liquid used to coat the inside of organs so that they will show up on an X-ray. A series of x-rays are taken to evaluate what happens as the liquid is swallowed.
- Radioisotope gastric-emptying scan: during this test, the patient eats food containing a radioisotope. The dosage of radiation from the radioisotope is very small and not harmful, but allows the radiologist to see the food in the stomach and how quickly it leaves the stomach.
- Ultrasound: ultrasound is a diagnostic imaging technique which uses high-frequency sound waves and a computer to create images of blood vessels, tissues, and organs. Ultrasounds are used to view internal organs as they function, and to assess blood flow through various vessels. Gel is applied to the area of the body being studied, such as the abdomen, and a transducer placed on the skin. The transducer sends sound waves into the body that bounce off organs and return to the ultrasound machine, producing an image on the monitor.
- Upper GI series (also called barium swallow): the upper GI series is a diagnostic test that examines the organs of the upper part of the digestive system: the esophagus, stomach, and duodenum (the first section of the small intestine). Barium is swallowed and X-rays are then taken to evaluate the digestive organs. The same drawbacks of radiological detection debilitate this test as well.

Endoscopic procedures:

- Colonoscopy: colonoscopy is a procedure that allows a view of the entire length of the large intestine, and can often help identify abnormal growths, inflamed tissue, ulcers, and bleeding. It involves inserting a colonoscope, a long, flexible, lighted tube, in through the rectum up into the colon. The colonoscope allows the physician to see the lining of the colon, remove tissue for further examination, and possibly treat some problems that are discovered.
- Endoscopic retrograde cholangiopancreatography (ERCP): ERCP is a procedure that allows the physician to diagnose and treat problems in the liver, gallbladder, bile ducts, and pancreas. The procedure combines X-ray and the use of an endoscope. The scope is guided through the patient's mouth and throat, then through the esophagus, stomach, and duodenum. The physician can examine the inside of these organs and detect any abnormalities. A tube is then passed through the scope, and a dye is injected which will allow the internal organs to appear on an X-ray.
- Esophagogastroduodenoscopy (also called EGD, or upper endoscopy): an EGD is a procedure that allows the examination of the inside of the esophagus, stomach, and duodenum. An endoscope is guided into the mouth and throat, then into the esophagus, stomach, and duodenum, and allows a view of the inside of this area of the body, as well as the insertion of instruments for the removal of a sample of tissue for biopsy, if necessary.
- Sigmoidoscopy: diagnostic procedure that allows the examination of the inside of a portion of the large intestine. It is helpful in identifying the causes of diarrhea, abdominal pain, constipation, abnormal growths, and bleeding. A sigmoidoscope is inserted into the intestine through the rectum. The scope blows air into the intestine to inflate it and make viewing the inside easier.

Other procedures:

- Anorectal manometry: this test helps determine the strength of the muscles in the rectum and anus. These muscles normally tighten to hold in a bowel movement and relax when a bowel movement is passed. Anorectal manometry is helpful in evaluating anorectal malformations and Hirschsprung's disease,

among other problems. A small tube is placed into the rectum to measure the pressures exerted by the sphincter muscles that ring the canal.

- Esophageal manometry: this test helps determine the strength of the muscles in the esophagus. It is useful in evaluating gastroesophageal reflux and swallowing abnormalities. A small tube is guided into the nostril, then passed into the throat, and finally into the esophagus, and the pressure of the esophageal muscles is then measured.

- pH monitoring: an esophageal pH monitor is helpful in evaluating gastroesophageal reflux disease (GERD). A thin, plastic tube is placed into a nostril, guided down the throat, and then into the esophagus. The tube stops just above the lower esophageal sphincter, which is at the connection between the esophagus and the stomach. At the end of the tube inside the esophagus is a sensor that measures pH. The other end of the tube outside the body is connected to a monitor that records the pH levels for a 12 to 24 hour period. Normal activity is encouraged during the study, and a diary is kept of symptoms experienced, or activity that might be suspicious for reflux, such as gagging or coughing.

- Gastric manometry: this test measures electrical and muscular activity in the stomach. A thin tube is passed down the patient's throat into the stomach. This tube contains a wire that takes measurements of the electrical and muscular activity of the stomach as it digests foods and liquids. This helps show how the stomach is working, and if there is any delay in digestion.

Despite all these procedures, there is still a need for an improved method of diagnostic that enables imaging of the entire GI tract in a controllable manner. Thus, it is an object of the present invention to provide a diagnostic gastro-retentive device which may be retained in the stomach for a period of time longer than the physiological gastric emptying time, and its transit may be followed from the stomach to the colon with high resolution and negligible interference.

Other uses and objects of the invention will become clear as the description proceeds.

Summary of the Invention

The invention relates to a gastro-retentive diagnostic device for use in the diagnosis of pathological and physiological conditions of the gastrointestinal (GI) tract, wherein said device comprises a detectable diagnostic agent and is retained in the stomach for a period of time longer than the physiological gastric emptying, when ingested following fast or a low calorie meal, said period of time being between 3 and 24 hours, and wherein said device is comprised of:

a) a single- or multi-layered matrix having a two- or three-dimensional geometric configuration comprising a polymer that does not retain in the stomach more than a conventional dosage form, said polymer selected from the group consisting of:

(1) a degradable polymer selected from:

(i) a hydrophilic polymer which is not instantly soluble in gastric fluids;

(ii) an enteric polymer substantially insoluble at pH less than 5.5;

(iii) an enteric polymer substantially insoluble at pH less than 4.5;

(iv) a hydrophobic polymer; and

(v) any mixture of at least two polymers as defined in (i), (ii), (iii) or (iv); or any chemical or physical cross linking product of said mixtures

(2) a non-degradable polymer;

(3) a mixture of at least one polymer as defined in (1) with at least one polymer as defined in (2); or any chemical or physical cross linking of said mixtures;

b) a continuous or non-continuous membrane, that does not retain in the stomach more than a conventional unit form, affixed or attached to said matrix, said membrane comprising at least one polymer having a substantial mechanical strength; and

c) a diagnostic agent or device embedded in a layer of said matrix, or being entrapped between at least two layers of said matrix, or being contained in a carrier, or being contained in a carrier attached to said membrane as defined in (b).

The said diagnostic agent may be contained in a suitable carrier, particularly, but not limited to, a polymeric matrix, bead, tablet, capsule or any solid unit form.

The diagnostic device of the invention may further comprise a shielding layer covering at least one face of said matrix, optionally covering all or part of said membrane, said shielding layer comprising a polymer that does not retain in the stomach more than a conventional dosage form, said polymer being selected from the group consisting of:

(a) a hydrophilic polymer which is not instantly soluble in gastric fluids;

(b) an enteric polymer substantially insoluble at pH less than 5.5;

(c) an enteric polymer substantially insoluble at pH less than 4.5;

(d) a hydrophobic polymer; and

(e) any mixture of at least two polymers as defined in (a), (b), (c) or (d); or any chemical or physical cross linking product of said mixtures

The gastro-retentive diagnostic device of the invention is further characterized in that its shape and/or size may change upon contact with gastrointestinal fluids. In particular, changes may be achieved by said polymeric matrix being foldable, rollable, inflatable and/or swellable. Specifically, the dimensions of the device of the invention can increase by at least 10 percent upon contact with gastrointestinal fluids.

Of particular interest is a gastro-retentive diagnostic device of the invention wherein its dimensions as obtained in the gastric lumen are preserved while in the GI tract until reaching the distal parts of the colon.

In a particular embodiment, the diagnostic agent of the gastro-retentive diagnostic device of the invention is retained in said carrier during its transit along the GI tract.

In another preferred embodiment, the diagnostic agent in the gastro-retentive diagnostic device of the invention is released from said carrier in a controlled-release manner during its transit along the GI tract.

The said hydrophilic polymer is preferably selected from the group consisting of: a protein, a polysaccharide, a starch, a polyacrylate, a hydrogel-forming polymer, a polyvinyl alcohol or polyvinyl pyrrolidone, a polyethylene oxide, derivatives of such hydrophilic polymers and any mixture thereof. More particularly, the hydrophilic polymer is one of hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, methyl cellulose, maltodextrin, sodium alginate, pre-gelatinized starch and guar gum.

Alternatively, the hydrophilic polymer may be cross-linked with a suitable cross-linking agent, for example, glutaraldehyde.

In a specific embodiment the hydrophilic polymer is an enzymatically hydrolyzed cross-linked gelatin or derivative thereof.

The enteric polymer may be selected from shellac, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose acetate succinate and methylmethacrylate-methacrylic acid copolymers. Particularly, the said enteric polymer may be

methylmethacrylate-methacrylic acid copolymer having a ratio of ester to free carboxylic groups of 2:1.

The said shielding layer may comprise a mixture of said hydrophilic polymer and said enteric polymer.

The said substantially hydrophobic polymer may be ethylcellullose, a copolymer of acrylic acid and methacrylic acid esters, having from about 5 to 10% functional quaternary ammonium groups, polyethylene, polyamide, polyvinylchloride, polyvinyl acetate, methylmethacrylate methacrylic acid copolymers, methylmethacrylate methacrylic acid copolymers, modified with dimethylaminoethyl moieties, and/or any mixtures thereof.

The said membrane may be selected from the group consisting of hydrophobic non-degradable polymers, hydrophobic degradable polymers and mixtures thereof. In particular embodiments, the membrane is comprised of a mixture of 1-poly(lactic acid) (1-PLA) and ethylcellulose at a ratio of 9:1, respectively.

The said anti-adhering layer may be selected from the group consisting of a pharmaceutically acceptable cellulose or derivative thereof, silicate or talc, preferably microcrystalline cellulose.

The diagnostic device of the invention may further comprise a plasticizer, which may be an ester selected from the group consisting of phthalate esters, phosphate esters, citrate esters, fatty acid esters and tartarate esters, free fatty acids or alcohols, glycerine or glycol derivatives, ethylene oxide derivatives or sorbitol.

The gastro-retentive diagnostic device of the invention may be folded into a capsule, preferably a soft gel capsule.

The gastro-retentive diagnostic device of the invention is particularly useful in the diagnosis or monitoring of pathological conditions of the GI tract, specifically, but not limited to gastritis, gastroenteritis, ulcer, colitis, diverticulosis, colon cancer, carcinoid, inflammatory bowel disease, gastrointestinal obstructions, metabolic diseases associated with excess or deficient secretion of gut hormones such as gastrin, motilin, cholicytokinin (CCK), somatostatin, secretin, vasoactive intestinal peptide (VIP), galanin, geralin, and enzymes such as amylase, lipase, pepsins, chymotrypsin and trypsin.

The said diagnostic agent may be selected from black iron oxide, radioactive isotopes, radioactive isotope labeled material which is capable of specific binding to gastrointestinal lumen components such as somatostatin receptors, opiate receptors and neurokinin receptors, radioactive isotope labeled material which is not significantly absorbed in the GI tract such as Octeoscran®, radioactive isotope labeled material which is analogous to bioactive materials or their precursors such as antibodies, proteins, peptides, amino acids, triglycerides, fatty acids, carbohydrates, and mono and disaccharides, and oligosaccharides.

The said diagnostic means to be used with the device of the present invention may be any one of MRI, CT, X-ray, ultrasound and gamma scintigraphy.

The gastro-retentive diagnostic device of the invention may be used in the determination of the integrity of the intestinal lumen.

The gastro-retentive diagnostic device of the invention may optionally further comprise at least one of telemetry device, memory device, a pH-sensitive device, a blood-detecting device and a pressure-sensitive device.

The invention also relates to the use of the present gastro-retentive diagnostic device for functional imaging of the GI tract components and/or for evaluating GI transit time in a subject in need.

In yet a further embodiment, the invention relates to a diagnostic method for GI tract conditions, comprising administering the gastro-retentive diagnostic device of the invention and tracing its trail through the GI tract with the assistance of imaging diagnostic means.

Alternatively, the invention relates to a diagnostic method for GI tract conditions, comprising administering the gastro-retentive diagnostic device of the invention and tracing the trail of said released diagnostic agent through the GI tract with the assistance of imaging diagnostic means.

Brief Description of the Figures

Figure 1: MRI of human subject 10 minutes after breakfast (282 kcal). The stomach is marked by a red line. Representative picture of coronal images.

Figure 2: MRI of human subject 20 minutes after breakfast (282 kcal). The GRDF (magnetite incorporated in substantially hydrophobic inner membrane) was taken 10 minutes before imaging.

Figure 3: MRI of the same human subject (as depicted in Figs. 1 and 2) 10 hours after oral administration of GRDF (magnetite incorporated in substantially hydrophobic inner membrane).

Figure 4: MRI of the same human subject (as depicted in Figs. 1-3), 24 hours after oral administration of GRDF (magnetite incorporated in substantially hydrophobic inner membrane).

Figure 5: MRI of human stomach after low-calorie meal. Representative picture of axial images.

Figure 6: MRI of human stomach after low-calorie meal, after administration of GRDF with hydrophilic inner membrane, which enables the control release of magnetite. Representative picture of axial images.

Detailed Description of the Invention

Although there have been many developments in the field of detection of abnormalities and afflictions of the GI tract, there are still shortcomings that hamper the capability of providing precise diagnostic evaluation in a patient-friendly way. These mainly include the interference caused by air during MRI imaging of the intestine, the inability to achieve continuous release of contrast agent to the intestine for a sufficient time duration.

The present inventors have explored the use, as a diagnostic device, of a gastroretentive drug delivery system previously described in co-owned US 6,685,962.

Thus, in a first aspect, the present invention provides a gastro-retentive diagnostic device for use in the diagnosis of pathological and physiological conditions of the GI tract, wherein said device comprises a detectable diagnostic agent and is retained in the stomach for a period of time longer than the physiological gastric emptying and gastrointestinal transit time, when ingested following fast or a low calorie meal, said period of time being between 3 and 24 hours, and wherein said device is comprised of:

a) a single- or multi-layered matrix having a two- or three-dimensional geometric configuration comprising a polymer that does not retain in the stomach more than a conventional dosage form, said polymer selected from the group consisting of:

(1) a degradable polymer selected from:

(i) a hydrophilic polymer which is not instantly soluble in gastric fluids;

(ii) an enteric polymer substantially insoluble at pH less than 5.5;

(iii) an enteric polymer substantially insoluble at pH less than 4.5;

(iv) a hydrophobic polymer; and

(v) any mixture of at least two polymers as defined in (i), (ii), (iii) or (iv); or any chemical or physical cross linking of said mixtures

(2) a non-degradable polymer;

(3) a mixture of at least one polymer as defined in (1) with at least one polymer as defined in (2); or any chemical or physical cross linking product of said mixtures

b) a continuous or non-continuous membrane, that does not retain in the stomach more than a conventional unit form, affixed or attached to said matrix, said membrane comprising at least one polymer having a substantial mechanical strength; and

c) a diagnostic agent or device embedded in a layer of said matrix, or being entrapped between at least two layers of said matrix, or being contained in a carrier, or being contained in a carrier attached to said membrane as defined in (b).

In one specific embodiment of said diagnostic device, said diagnostic agent is contained in a suitable carrier, which may be one of polymeric matrices, beads, tablets, capsules and any solid unit form.

Various diagnostic agents may be used with the diagnostic device of the invention, e.g. black iron oxide (magnetite), radioactive isotope, radioactive isotope labeled material which is capable of specific binding to gastrointestinal lumen components such as somatostatin receptors, opiate receptors and neurokinin receptors, radioactive isotope labeled material which is not significantly absorbed in the GI tract such as Octeoscran®, radioactive isotope labeled material which is analogous to bioactive materials or their precursors such as antibodies, proteins, peptides, amino acids, triglycerides, fatty acids, carbohydrates, and mono and disaccharides.

In another embodiment the diagnostic device of the invention further comprises a shielding layer covering at least one face of said matrix, optionally covering all or part of said membrane. Said shielding layer comprises a polymer that does not retain in the stomach more than a conventional dosage form, said polymer being selected from the group consisting of: a hydrophilic polymer which is not instantly soluble in gastric fluids, an enteric polymer substantially insoluble at pH less than 5.5, a hydrophobic polymer and any mixture thereof. Preferably, said shielding layer comprises a mixture of said hydrophilic polymer and said enteric polymer.

In another specific embodiment of the present invention, the shape and/or size of the gastro-retentive diagnostic device changes upon contact with gastrointestinal fluids. Said change in shape and/or size may be produced by different means. For example, the polymeric matrix is inflatable and/or swellable, whereas the beads, tablets and other solid unit forms are inflatable and/or swellable, upon contact with gastrointestinal fluids. In addition, the dimensions of the device may increase by at least 10 percent upon contact with gastrointestinal fluids due to mechanical strength endowed by the elasticity of the polymer comprising the gastro-retentive diagnostic device.

Furthermore, said polymeric matrix is foldable and/or rollable, enabling said device to be folded into a capsule, preferably a soft gel capsule.

It is important to note that one of the advantages of the gastroretentive diagnostic device of the invention is that the dimensions obtained in the gastric lumen are preserved while in the GI tract until reaching the distal parts of the colon.

In a further specific embodiment of the gastro-retentive diagnostic device of the invention, said hydrophilic polymer is selected from the group consisting of: a protein, a polysaccharide, a starch, a polyacrylate, a hydrogel-forming polymer,

a polyvinyl alcohol or polyvinyl pyrrolidone, a polyethylene oxide, derivatives of such hydrophilic polymers and any mixture thereof. More specifically, said hydrophilic polymer is one of hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, methyl cellulose, maltodextrin, sodium alginate, pre-gelatinized starch and guar gum.

Said hydrophilic polymer may be cross-linked with a suitable cross-linking agent, e.g. glutaraldehyde. Alternatively, said hydrophilic polymer is an enzymatically hydrolyzed cross-linked gelatin or derivative thereof.

In a yet further embodiment, said enteric polymer is selected from the group consisting of shellac, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate or methylmethacrylate- methacrylic acid copolymers. Preferably, said enteric polymer is methylmethacrylate-methacrylic acid copolymer having a ratio of ester to free carboxylic groups of 2:1.

In an even further embodiment of the gastro-retentive diagnostic device of the invention, said substantially hydrophobic polymer is selected from the group consisting of ethylcellullose, a copolymer of acrylic acid and methacrylic acid esters, having from about 5 to 10 % functional quaternary ammonium groups, polyethylene, polyamide, polyvinylchloride, polyvinyl acetate, polymethyl methacrylate-polymethyl methacrylic acid copolymer, or polymethyl methacrylate-polymethyl methacrylic acid copolymer with dimethylaminoethyl methacrylate functional group, and any mixtures thereof.

Yet another embodiment of the invention refers to the membrane of the diagnostic device, wherein said membrane is selected from the group consisting of non-degradable polymers, degradable polymers and mixtures thereof. Preferably, said membrane is comprised of a mixture of 1-poly(lactic acid) (1-PLA) and ethylcellulose at a ratio of 9:1, respectively.

The diagnostic device of the present invention also comprises an anti-adhering layer, affixed to at least one outer face thereof. Said anti-adhering layer may be selected from the group consisting of a pharmaceutically acceptable cellulose or derivative thereof, silicate, talc, and an enteric polymer substantially insoluble at pH less than about 5.5. Preferably, said anti-adhering layer is microcrystalline cellulose.

The diagnostic device of the invention further comprises a plasticizer, wherein said plasticizer is an ester selected from the group consisting of phthalate esters, phosphate esters, citrate esters, fatty acid esters and tartarate esters, free fatty acids or alcohols, glycerine or glycol derivatives, ethylene oxide derivatives, or sorbitol, preferably glycerine

The gastro-retentive diagnostic device of the invention is suitable for use in any pathological condition of the GI tract, particularly for gastritis, gastroenteritis, ulcer, colitis, diverticulosis, colon cancer, carcinoid, inflammatory bowel disease, gastrointestinal obstructions, metabolic diseases associated with excess or deficient secretion of gut hormones such as gastrin, motilin, cholicytokinin (CCK), somatostatin, secretin, vasoactive intestinal peptide (VIP), galanin, geralin, and enzymes such as amylase, lipase, pepsins, chymotrypsin and trypsin.

The gastro-retentive diagnostic device of the invention is to be used with any diagnostic procedure that allows the imaging of the GI tract, e.g. MRI, CT, X-ray, gamma scintigraphy or ultrasound. Preferably the diagnostic device of the invention is to be used with MRI.

One of the most important applications of the gastro-retentive diagnostic device of the invention is its use in the determination of the integrity of the intestinal lumen. Very few devices have been described so far that allow such analysis. Mostly, devices allow the visualization of the stomach and the small

intestine, or the colon, but not of the full-length intestine. In contrast, the diagnostic device described herein, in combination with the appropriate equipment (MRI, CT, etc.) may be visualized throughout its journey in the GI tract, starting from the stomach, followed by the small intestine (the duodenum, jejunum and ileum), and then the large intestine (the cecum, the ascending, transverse, descending and sigmoid colon).

In a last embodiment, the gastro-retentive diagnostic device of the invention may optionally further comprise at least one of a telemetry device, a memory device, a pH-sensitive device, a blood-detecting device and a pressure-sensitive device.

Hence, another aspect of the present invention is the use of the gastro-retentive diagnostic device for functional imaging of the GI tract components, as well as for evaluating GI transit time in a subject in need.

The gastro-retentive diagnostic device for the present invention, as described herein above, incorporates two main separate embodiments. In the first, the diagnostic agent is essentially retained or contained in said carrier during its transit along the GI tract, i.e, there is no leakage or release of the diagnostic agent. In the second, said diagnostic agent is released from said carrier in a controlled-release manner during its transit along the GI tract.

As shown in the accompanying examples, by using the diagnostic device which bears MRI tracer such as magnetite, the gastric emptying of the device was followed throughout the GI tract. In the present example, the inner membrane of the device was of substantially hydrophobic composition which maintained the MRI tracer (magnetite) within the intact device, thus enabling to image by MRI the transit of said device from the stomach to the colon with high resolution and negligible interference.

Alternatively, a device comprising a hydrophilic inner membrane could be used for the controlled release of the tracer from the stomach for a prolonged period of time. In this case, by using MRI (or gamma scintigraphy for radioactive isotopes or X-ray for metal contrast) the GI transit time can be measured, providing a clear indication of the physiological versus patho-physiological conditions of the GI tract.

In a final aspect, the present invention provides a diagnostic method for GI tract conditions, said method comprising administering the gastro-retentive diagnostic device and tracing its trail through the GI tract with the assistance of imaging diagnostic means. The trail to be traced is that of the device itself, when the device retains the diagnostic agent throughout its journey through the GI tract.

Alternatively, the trail to be traced is that of the diagnostic agent which is released from the diagnostic device.

Alternatively, the device can be equipped with suitable probe for the abovementioned applications, and a radiotelemetry component to transmit the collectable data to an external data logger. An internal memory chip can also be incorporated to facilitate the actions or to store the data until retrieved from the investigated subject.

The diagnostic method utilizes as diagnostic means any apparatus that allows visualization of the GI tract, e.g. MRI, CT, X-ray, ultrasound or gamma scintigraphy.

The present invention is defined by the claims, the contents of which are to be read as included within the disclosure of the specification.

Disclosed and described, it is to be understood that this invention is not limited to the particular examples, process steps, and materials disclosed herein as

such process steps and materials may vary somewhat. It is also to be understood that the terminology used herein is used for the purpose of describing particular embodiments only and not intended to be limiting since the scope of the present invention will be limited only by the appended claims and equivalents thereof.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The following Examples are representative of techniques employed by the inventors in carrying out aspects of the present invention. It should be appreciated that while these techniques are exemplary of preferred embodiments for the practice of the invention, those of skill in the art, in light of the present disclosure, will recognize that numerous modifications can be made without departing from the spirit and intended scope of the invention.

Examples

Example 1: Preparation of the inner membrane of the gastro-retentive diagnostic device (GRDD), containing tracer

Hydrophylic membranes:

The GRDD inner membrane may be prepared as hydrophilic, in which case the marker is prone to leak, leaving a trail that may be traced.

Hydrophylic membranes were prepared with hydroxypropyl cellulose film, which is capable of complete dissolution under physiological conditions, enabling leaking of the marker by its mechanical dislodging from the device, probably via channels in the outer membrane. The formulation of hydrophilic membranes is shown below:

- Hydroxypropyl cellulose (Klucel® EF, Hercules), 95 g
- Black iron oxide, 5 g
- Distilled water, up to 1 liter

The polymer was dissolved in water, and black iron oxide was introduced and stirred till homogeneity. The dispersion was then cast onto trays and dried in an oven.

The hydrophilic membrane may also be prepared in an ethanol base, as follows:

- Klucel® EF, 98 g
- Black iron oxide, 2 g
- Ethanol USP up to 1 liter

- *Substantially hydrophobic membranes*

The substantially hydrophobic membrane is a polymer which may be plasticized with acceptable materials. This membrane remains intact and does not change its mechanical properties upon exposure to the physiological conditions of the stomach for at least 24 hours. The formulation of hydrophobic membranes is shown below:

- polymethyl methacrylate-polymethyl methacrylic acid copolymer (1;1) (Eudragit® L, Roehm) 57 g
- PEG 20,000 (Fluka) 38 g
- Black iron oxide (Aldrich) 5 g
- Ethanol USP up to 700 ml

The hydrophobic membrane may also be prepared with ethyl cellulose, as follows:

- Eudragit® L 49.25 g

- Ethyl cellulose N100 19.7 g
- Triacetin 29.55 g
- Black iron oxide 1.5 g
- Ethanol USP ad 700 ml

Example 2: Use of GRDD with MRI in human subjects

- *Study Protocol*:

In a Helsiki approved study conducted in two Israeli hospitals, informed volunteers (of both genders, total n=30) were requested to fast the night before the experiment (8 to 12 hours fast). The GRDF was taken with a glass of water immediately after eating a standardized low calorie (282 Kcal) meal.

Imaging: Retention of the GRDD capsule in the stomach was assessed by MRI at various time-points

Details of MRI procedure:

1. localizer (0:56 min)

2. FSPGR, Axial: (1:41 min), FOV: 40X40 cm; matrix size: 256X160; slice thickness: 6mm X 1mm spacing; TE/TR=minimum/125; flip angle=80; BW=31.25; 5 NEX.

3. FSPGR, Coronal: (1:41 min); FOV: 46X46 cm; matrix size:256X160; slice thickness: 6mm X 1mm spacing; TE/TR=minimum/125; flip angle=80; BW=31.25; 5 NEX.

Claims:

1. A gastro-retentive diagnostic device for use in the diagnosis of pathological and physiological conditions of the gastrointestinal (GI) tract, wherein said device comprises a detectable diagnostic agent and is retained in the stomach for a period of time longer than the physiological gastric emptying, when ingested following fast or a low calorie meal, said period of time being between 3 and 24 hours, and wherein said device is comprised of:

a. a single- or multi-layered matrix having a two- or three-dimensional geometric configuration comprising a polymer that does not retain in the stomach more than a conventional dosage form, said polymer selected from the group consisting of:

(1) a degradable polymer selected from:

(i) a hydrophilic polymer which is not instantly soluble in gastric fluids;

(ii) an enteric polymer substantially insoluble at pH less than 5.5;

(iii) an enteric polymer substantially insoluble at pH less than 4.5;

(iv) a hydrophobic polymer; and

(v) any mixture of at least two polymers as defined in (i), (ii), (iii) or (iv); or any chemical or physical cross linking product of said mixtures

(2) a non-degradable polymer;

(3) a mixture of at least one polymer as defined in (1) with at least one polymer as defined in (2); or any chemical or physical cross linking of said mixtures;

b) a continuous or non-continuous membrane, that does not retain in the stomach more than a conventional unit form, affixed or attached to said matrix, said membrane comprising at least one polymer having a substantial mechanical strength; and

c) a diagnostic agent or device embedded in a layer of said matrix, or being entrapped between at least two layers of said matrix, or being contained in a carrier, or being contained in a carrier attached to said membrane as defined in (b).

2. The gastro-retentive diagnostic device of claim 1, wherein said diagnostic agent is contained in a suitable carrier.

3. The gastro-retentive diagnostic device of claim 2, wherein said carrier is one of polymeric matrices, beads, tablets, capsules and any solid unit form.

4. The diagnostic device of any one of claims 1 to 3, further comprising a shielding layer covering at least one face of said matrix, optionally covering all or part of said membrane, said shielding layer comprising a polymer that does not retain in the stomach more than a conventional dosage form, said polymer being selected from the group consisting of:
(a) a hydrophilic polymer which is not instantly soluble in gastric fluids;
(b) an enteric polymer substantially insoluble at pH less than 5.5;
(c) an enteric polymer substantially insoluble at pH less than 4.5;
(d) a hydrophobic polymer; and
(e) any mixture of at least two polymers as defined in (a), (b), (c) or (d); or any chemical or physical cross linking product of said mixtures

5. The gastro-retentive diagnostic device of any one of claims 1 to 4, wherein the shape and/or size of said device changes upon contact with gastrointestinal fluids.

6. The gastro-retentive diagnostic device of any one of claims 4 and 5, wherein said polymeric matrix is foldable, rollable, inflatable and/or swellable.

7. The gastro-retentive diagnostic device of any one of claims 1 to 6, wherein the dimensions of the device can increase by at least 10 percent upon contact with gastrointestinal fluids.

8. The gastro-retentive diagnostic device of any one of the preceding claims, wherein the dimensions of said device as obtained in the gastric lumen are preserved while in the GI tract until reaching the distal parts of the colon.

9. The gastro-retentive diagnostic device of any one of claims 1 to 8, wherein said diagnostic agent is retained in said carrier during its transit along the GI tract.

10. The gastro-retentive diagnostic device of any one of claims 1 to 8, wherein said diagnostic agent is released from said carrier in a controlled-release manner during its transit along the GI tract.

11. The gastro-retentive diagnostic device of any one of the preceding claims, wherein said hydrophilic polymer is selected from the group consisting of: a protein, a polysaccharide, a starch, a polyacrylate, a hydrogel-forming polymer, a polyvinyl alcohol or polyvinyl pyrrolidone, a polyethylene oxide, derivatives of such hydrophilic polymers and any mixture thereof.

12. The gastro-retentive diagnostic device of claim 11, wherein said hydrophilic polymer is one of hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, methyl cellulose, maltodextrin, sodium alginate, pre-gelatinized starch and guar gum.

13. The diagnostic device of any one of the preceding claims, wherein said hydrophilic polymer is cross-linked with a suitable cross-linking agent.

14. The diagnostic device of claim 13, wherein said cross-linking agent is glutaraldehyde.

15. The diagnostic device of any one of claims 1 to 12, wherein said hydrophilic polymer is an enzymatically hydrolyzed cross-linked gelatin or derivative thereof.

16. The gastro-retentive diagnostic device of any one of the preceding claims, wherein said enteric polymer is selected from the group consisting of shellac, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose acetate succinate and methylmethacrylate- methacrylic acid copolymers.

17. The diagnostic device of claim 16, wherein said enteric polymer is methylmethacrylate-methacrylic acid copolymer having a ratio of ester to free carboxylic groups of 2:1.

18. The diagnostic device of any one of the preceding claims, wherein said shielding layer comprises a mixture of said hydrophilic polymer and said enteric polymer.

19. The gastro-retentive diagnostic device of any one claims 1 to 10, wherein said substantially hydrophobic polymer is selected from the group consisting of ethylcellullose, a copolymer of acrylic acid and methacrylic acid esters, having from about 5 to 10 % functional quaternary ammonium groups, polyethylene, polyamide, polyvinylchloride, polyvinyl acetate, methylmethacrylate- methacrylic acid copolymers, methylmethacrylate-methacrylic acid copolymers, modified with dimethylaminoethyl moieties, and any mixtures thereof.

20. The diagnostic device of any one of the preceding claims, wherein said membrane is selected from the group consisting of hydrophobic non-degradable polymers, hydrophobic degradable polymers and mixtures thereof.

21. The diagnostic device as claimed in claim 20, wherein said membrane is comprised of a mixture of 1-poly(lactic acid) (1-PLA) and ethylcellulose at a ratio of 9:1, respectively.

22. The diagnostic device as claimed in any one of the preceding claims, wherein said anti-adhering layer is selected from the group consisting of a pharmaceutically acceptable cellulose or derivative thereof, silicate or talc.

23. The diagnostic device of claim 22, wherein said anti-adhering layer is microcrystalline cellulose.

24. The diagnostic device of any one of the preceding claims, further comprising a plasticizer, wherein said plasticizer is an ester selected from the group consisting of phthalate esters, phosphate esters, citrate esters, fatty acid esters and tartarate esters, free fatty acids or alcohols, glycerine or glycol derivatives, ethylene oxide derivatives or sorbitol.

25. The diagnostic device of claim 24, wherein said plasticizer is glycerine

26. The gastro-retentive diagnostic device of any one of claims 1 to 25, folded into a capsule, preferably a soft gel capsule.

27. The gastro-retentive diagnostic device of any one of claims 1 to 25, wherein said device is a gastro-retentive inflatable or swellable tablet.

28. The gastro-retentive diagnostic device of any one of the preceding claims, wherein said pathological conditions of the GI tract may be selected from gastritis, gastroenteritis, ulcer, colitis, diverticulosis, colon cancer, carcinoid, inflammatory bowel disease, gastrointestinal obstructions, metabolic diseases associated with excess or deficient secretion of gut hormones such as gastrin, motilin, cholicytokinin (CCK), somatostatin,

secretin, vasoactive intestinal peptide (VIP), galanin, geralin, and enzymes such as amylase, lipase, pepsins, chymotrypsin and trypsin.

29. The gastro-retentive diagnostic device of any one of the preceding claims, wherein said diagnostic agent may be selected from black iron oxide, radioactive isotopes, radioactive isotope labeled material which is capable of specific binding to gastrointestinal lumen components such as somatostatin receptors, opiate receptors and neurokinin receptors, radioactive isotope labeled material which is not significantly absorbed in the GI tract such as Octeoscran®, radioactive isotope labeled material which is analogous to bioactive materials or their precursors such as antibodies, proteins, peptides, amino acids, triglycerides, fatty acids, carbohydrates, and mono and disaccharides, and oligosaccharides.

30. The gastro-retentive diagnostic device of any one of the preceding claims, wherein said diagnostic means is any one of MRI, CT, X-ray, ultrasound and gamma scintigraphy.

31. The gastro-retentive diagnostic device of any one of the preceding claims, for use in the determination of the integrity of the intestinal lumen.

32. The gastro-retentive diagnostic device of any one of the preceding claims, optionally further comprising a telemetry device.

33. The gastro-retentive diagnostic device of any one of the preceding claims, optionally further comprising a memory device.

34. The gastro-retentive diagnostic device of any one of the preceding claims, optionally further comprising a pH-sensitive device.

35. The gastro-retentive diagnostic device of any one of the preceding claims, optionally further comprising a blood-detecting device.

36. The gastro-retentive diagnostic device of any one of the preceding claims, optionally further comprising a pressure-sensitive device.

37. Use of the gastro-retentive diagnostic device of any one of the preceding claims, for functional imaging of the GI tract components.

38. Use of the gastro-retentive diagnostic device of any one of claims, for evaluating GI transit time in a subject in need.

39. A diagnostic method for GI tract conditions, said method comprising administering the gastro-retentive diagnostic device of any one of claims 1-9 and 11-36 and tracing its trail through the GI tract with the assistance of imaging diagnostic means.

40. A diagnostic method for GI tract conditions, said method comprising administering the gastro-retentive diagnostic device of any one of claims 10-36 and tracing the trail of said released diagnostic agent through the GI tract with the assistance of imaging diagnostic means.

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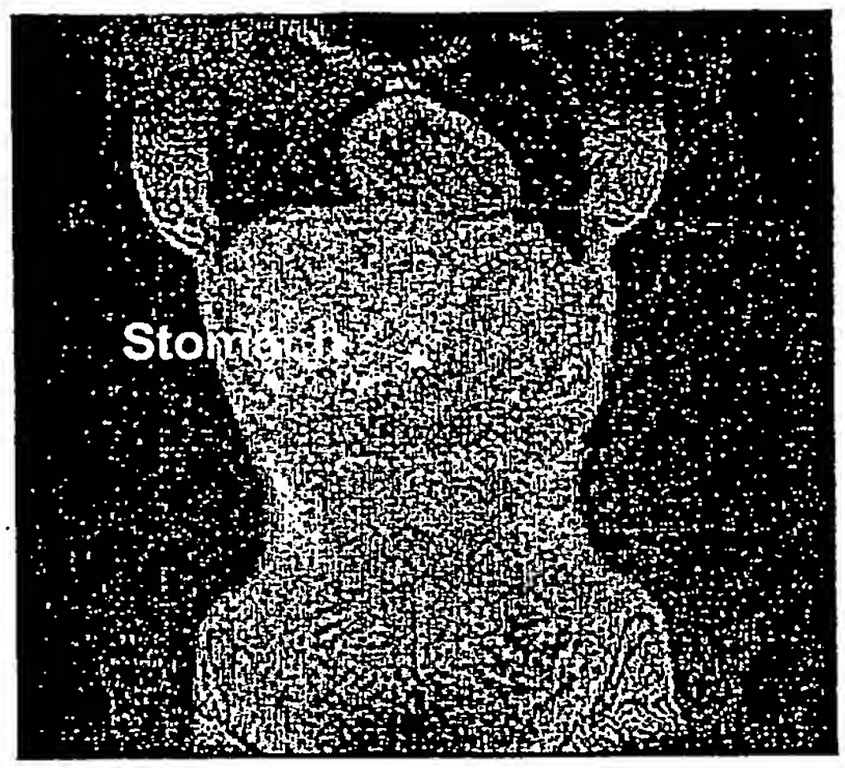

Fig. 1

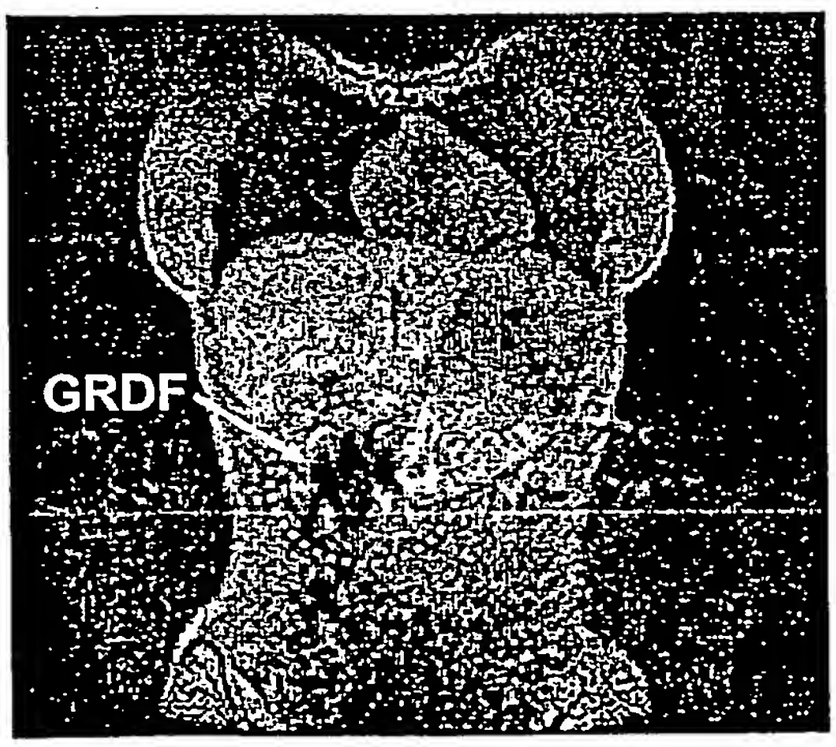

Fig. 2

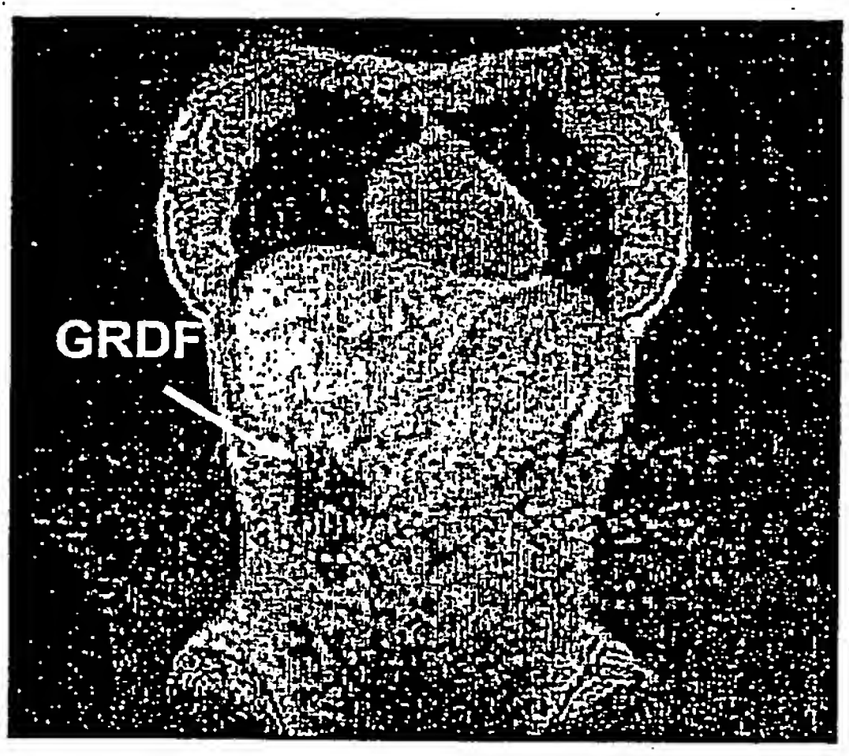

Fig. 3

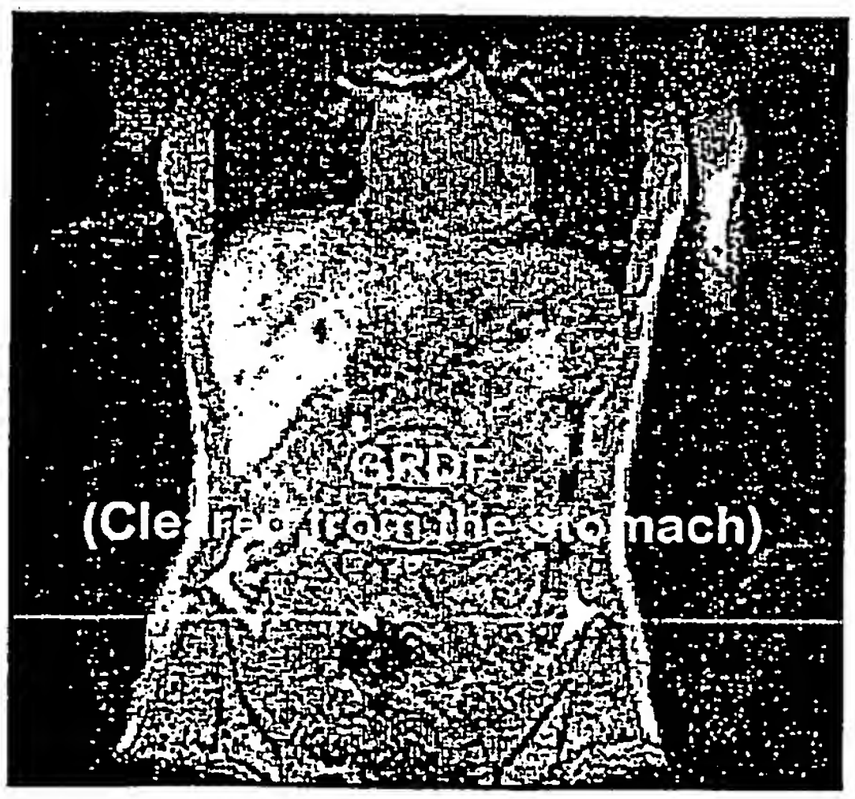

Fig. 4

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OF THE HEBREW UNIVERSITY OF JERUSALEM
AND INTEC PHARMA LTD.

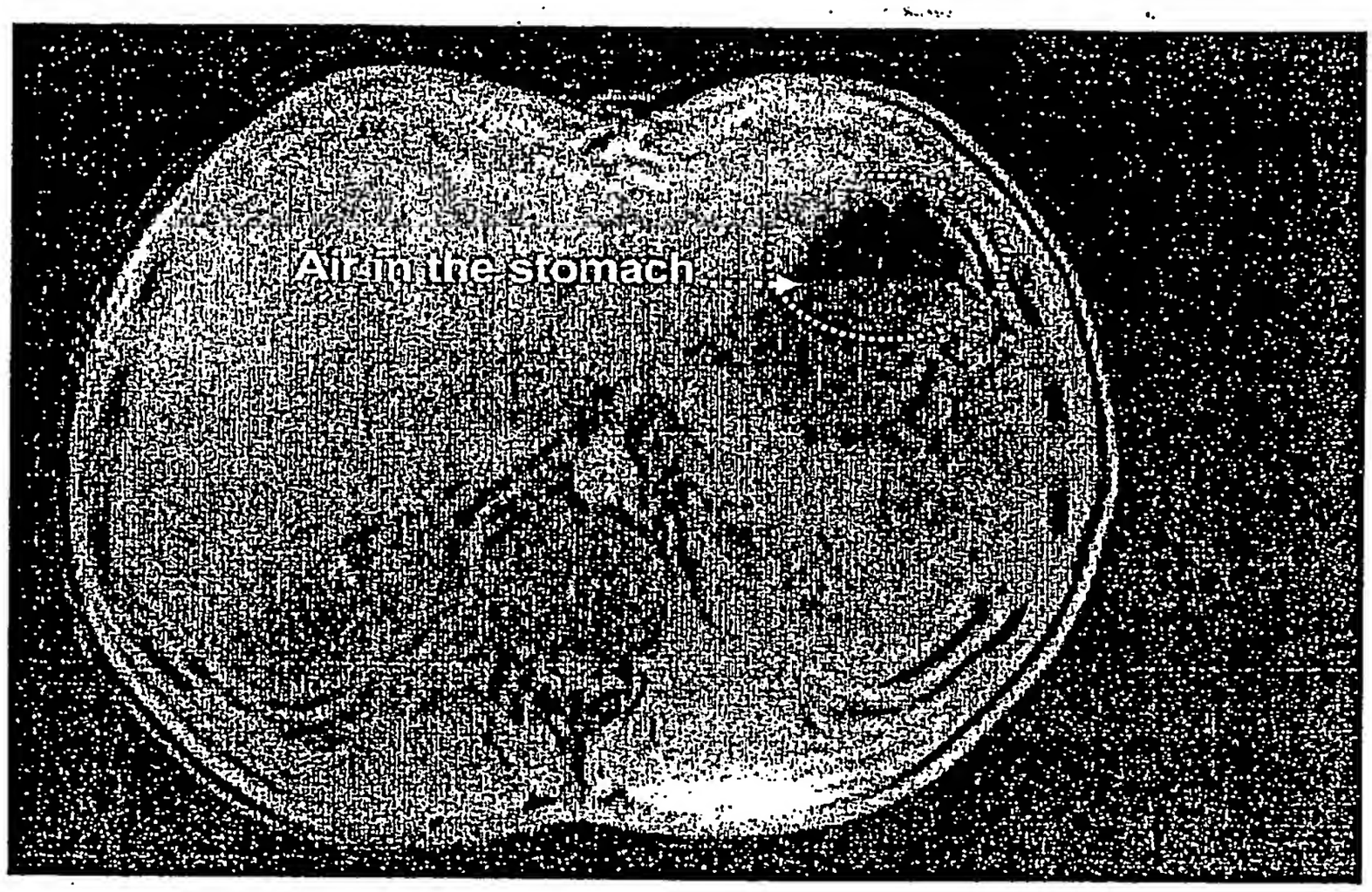

Fig. 5

YISSUM RESEARCH DEVELOPMENT COMPANY
OF THE HEBREW UNIVERSITY OF JERUSALEM
AND INTEC PHARMA LTD.

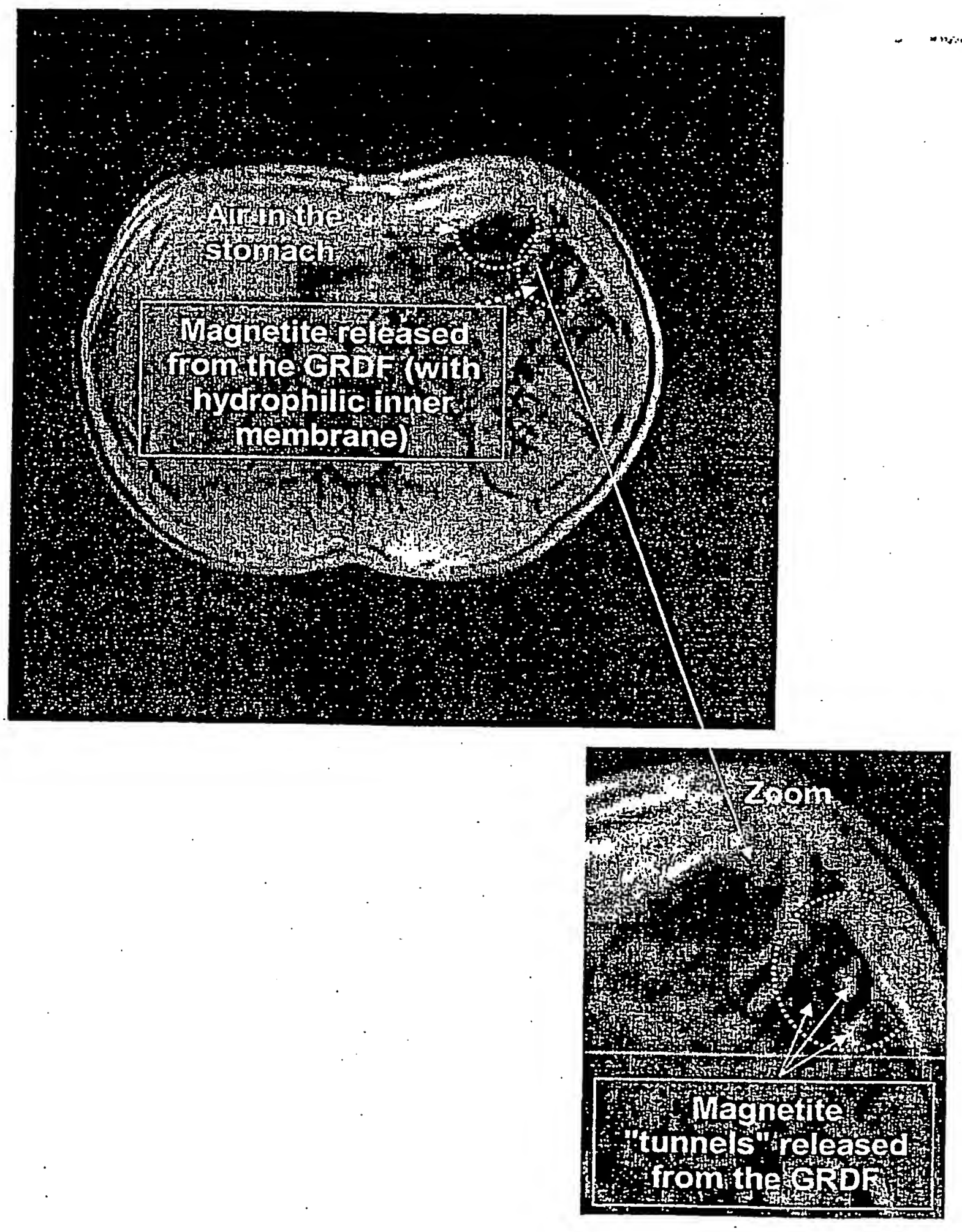

Fig. 6